PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference G 1758 PG	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/LV2004/000005	International filing date *(day/month/year)* 15.07.2004	Priority date *(day/month/year)* 04.08.2003
International Patent Classification (IPC) or national classification and IPC C07C243/12, C07C53/00, A61K31/205		
Applicant "JOINT STOCK COMPANY GRINDEKS" et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02.03.2005	20.12.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Lorenzo Varela, M.J. Telephone No. +49 89 2399-8239

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/LV2004/000005

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-12 as originally filed

   Claims, Numbers

   1-14 received on 12.07.2005 with letter of 12.07.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-14
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: US-A-5 017 611 (BREMANIS GUNAR A ET AL) 21 May 1991 (1991-05-21)
D2: WO 97/06795 A (KALVINSH IVARS ; VEVERIS MARIS (LV)) 27 February 1997 (1997-02-27)
D3: US-A-4 481 218 (ASTAPENOK ELENA B ET AL) 6 November 1984 (1984-11-06)
D4: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; AYUSHIEVA, S. TS. ET AL: "Iodide trimethylhydrazinium propionate in experimental hepatitis" XP002297883 retrieved from STN Database accession no. 2001:45250
D5: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; IL'INA, O. P. ET AL: "Efficacy of iodide trimethylhydrazonium propionate in the case of thyroid gland hypofunction" XP002297884 retrieved from STN Database accession no. 2000:710269
D6: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SHUTOV, G. K. ET AL: "Regulating lupine growth" XP002297885 retrieved from STN Database accession no. 1983:121372

1. The present application relates to meldonium salts of general formula $X^-(CH_3)_3N^+NHCH_2CH_2COOH$ wherein X^- is an anion selected from the group consisting of dihydrogen phosphate, hydrogen fumarate and orotate anions. Pharmaceutical compositions containing them, the use of the mentioned meldonium salts for the manufacture of pharmaceutical compositions as well as a process for producing the mentioned meldonium salts by treatment of meldonium in a solvent with the corresponding acid are claimed as well.

2. D1 discloses salts of meldonium ethyl esters wherein the anions are chloride, bromide or iodide and their use in the treatment of arrhythmia.

3. D2 discloses 3-(2,2,2-trimethylhydrazine)propionate and its use in the treatment of blood flow disorders.

4. D3 discloses 3-(2,2,2-trimethylhydryzinium)propionate and chloride, iodide, bromide or methanesulfonate salts of esters of 3-(2,2,2-trimethylhydryzinium)propionate. Its use as growth stimulator for animals and fowl are disclosed as well.

5. D4 discloses hydrazinium, 2-(2-carboxyethyl)-1,1,1-trimethyl-, iodide and its therapeutic, hepatoprotectoral effect.

6. D5 discloses hydrazinium, 2-(2-carboxyethyl)-1,1,1-trimethyl-, iodide and its therapeutic effect in the normalization of metabolism of the thyroid gland.

7. D6 discloses hydrazinium, 2-(2-carboxyethyl)-1,1,1-trimethyl-, iodide; hydrazinium, 2-(2-carboxyethyl)-1,1,1-trimethyl-, chloride; hydrazinium, 2-(2-carboxyethyl)-1,1,1-trimethyl-, (T-4)-tetraoxomolybdate(2-); hydrazinium, 2-(2-carboxyethyl)-1,1,1-trimethyl-, nitrate and hydrazinium, 2-(2-carboxyethyl)-1,1,1-trimethyl-, sulfate and their use in the regulation of lupine growth.

Novelty

8. The subject-matter of claims 1-14 is novel in the sense of Art. 33(2) PCT. None of the available documents of the prior art disclose the specific meldonium salts of general formula $X^-(CH_3)_3N^+NHCH_2CH_2COOH$ wherein X^- is an anion selected from the group consisting of dihydrogen phosphate, hydrogen fumarate and orotate anions (see paragraphs 2-7 above). Therefore, pharmaceutical compositions containing them, the use of the mentioned meldonium salts for the manufacture of pharmaceutical compositions as well as a process for producing the mentioned meldonium salts are novel as well.

Inventive step

9. The subject-matter of claims 1-14 involves an inventive step in the sense of Art. 33(3) PCT.

9.1. As acknowledged at pages 1 and 2 in the description (see D3-D6 as well), the

meldonium salts known in the prior art have the drawbacks consisting of high hygroscopicity and low stability.

9.2. The problem to be solved in the application can be seen in the provision of meldonium salts with improved properties.

9.3. The problem is solved with meldonium salts of general formula X^- $(CH_3)_3N^+NHCH_2CH_2COOH$ wherein X^- is an anion selected from the group consisting of dihydrogen phosphate, hydrogen fumarate and orotate anions which have lower hygroscopicity and toxicity than known meldonium salts. Hence, an inventive step is acknowledged.

Further comments

10. The examples 3 and 5-28 do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear, Article 6 PCT.

11. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1, D2 and D4-D6 is not mentioned in the description, nor are these documents identified therein.

12. The description has not been adapted to the amended claims.

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12.07.05
G 1758 PG

(NEW) CLAIMS

1. Meldonium salts having the general formula:

$$X^{\ominus}(CH_3)_3N^{\oplus}NHCH_2CH_2COOH$$

wherein $X^{\ominus}$ is an anion selected from the group consisting of dihydrogen phosphate, hydrogen fumarate and orotate anions.

2. A salt of claim 1 which is meldonium dihydrogen phosphate.

3. A salt of claim 1 which is meldonium hydrogen fumarate.

4. A salt of claim 1 which is meldonium orotate.

5. A process for producing the meldonium salts of any of claims 1 to 4 which process comprises

(a) dissolving in a manner known per se meldonium having the formula 3-(2,2,2-trimethyl hydrazinium) propionate in water or any other appropriate solvent;

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(b) adding an equimolar quantity of a polybasic acid selected from the group consisting of fumaric acid, phosphoric acid, and orotic acid;

(c) stirring the mixture at a temperature of from 20 to 50°C until the corresponding salt is formed; and

(d) evaporating the meldonium salt formed in step (c) to dryness, if necessary; and optionally recrystallising it from a suitable solvent.

6. A pharmaceutical composition comprising one of the salts of any of claims 1 to 5 as an active ingredient, which composition is intended for oral or sublingual administration and is in the form of tablets, with or without coating, capsules, caplets, dragees, granules, powder or solution, which composition contains from 0.5 to 5 g of the active ingredient in every tablet, capsule, dragee, granule or powder dose, or in the form of a 0.5-40% by weight solution or syrup for oral administration.

7. The pharmaceutical composition according to claim 6, wherein the pharmaceutically acceptable carrier is selected from the group consisting of one or more of the following members: stearic acid and its salts, lactose, glucose, saccharose, starch, talc, vegetable oils, polyethylene glycols, microcrystalline cellulose, aerosil, aromatizers, flavoring agents, colorants, ethyl alcohol and water.

8. A pharmaceutical composition comprising one of the salts of any of claims 1 to 5 as an active ingredient which composition is intended for parenteral administration and is in the form of a solution for injection, which composition contains from 0.5 to 40% by weight of the active ingredient and a pharmaceutically acceptable solvent.

9. The pharmaceutical composition according to claim 8, wherein the pharmaceutically acceptable solvent is selected from the group consisting of one or more of the following members: distilled water, isotonic solution, buffer solution and glucose solution.

10. A pharmaceutical composition comprising one of the salts of any of claims 1 to 5 as an active ingredient which composition is intended for transcutaneous ad-

ministration and is in the form of an ointment, cream, gel, solution or plaster, which composition contains from 0.5 to 40% by weight of the active ingredient and a pharmaceutically acceptable carrier.

11. The pharmaceutical composition according to claim 10, wherein the pharmaceutically acceptable carrier is selected from the group consisting of one or more of the following members: water, polyethylene glycols 400, 1500 and 4000, vegetable oils, fats, glycerine, preservants, emulgators, stabilizers, porous polymer material, dimethylsulphoxide, alcohol and water.

12. A pharmaceutical composition comprising one of the salts of any of claim 1 to 5 as an active ingredient which composition is intended for rectal administration and is in the form of suppositories or microenema, which composition contains from 0.5 to 40% by weight of the active ingredient and a pharmaceutically acceptable carrier.

13. The pharmaceutical composition according to claim 12, wherein the pharmaceutically acceptable carrier is selected from the group consisting of one or more of the following members: water, polyethylene glycols 400, 1500 and 4000, vegetable oils, fats, glycerine, preservants, emulgators and stabilizers.

14. Use of the meldonium salt of any of claims 1 to 5 for the manufacture of a pharmaceutical composition for once per day administration.
